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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/245,198	02/05/1999	JEFFREY BROWNING	A003	4642

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 01/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/245,198	BROWNING ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48-99* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *48,49,54,56,64,75-83,86-90,92-95,98 and 99* is/are allowed.

6)☒ Claim(s) *50-53,55,57-63,65-67,84,91,96 and 97* is/are rejected.

7)☒ Claim(s) *68-74 and 85* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *2/5/99* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 10/29/04 has been entered.

In an amendment filed 10/29/04, Applicant requested cancellation of claims 1-35 and addition of new claims 36-65. However, previously pending claims included claims 1-4, 6-8, 10, 28, 30, 31, and 39-47, and Applicant actually submitted new claims numbered 36-87. As such claims 1-4, 6-8, 10, 28, 30, 31, and 39-47 have been canceled and the newly submitted claims 36-87 have been renumbered as claims 48-99. See further below.

Claim Objections

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not). Applicant is required in response to this Action to submit properly numbered claims.

For the purpose of this Action, misnumbered claims 36-87 have been renumbered 48-99.

Claims 68-74 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims 68-74 have not been further treated on the merits.

Claim 85 is objected to because it is ungrammatical. Insertion of the word "said" between the words "isolating" and TRELL" is suggested.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 50, 53, 60, 62, 63, 65-67, and 91 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 50, 91, and 92 are indefinite because it is unclear what is intended by "amino acid terminus beginning at any one of amino acids 81-139 of SEQ ID NO:4." The term "amino acid terminus" is not a term of art. The Examiner believes Applicant intended "amino terminus". It is also unclear what is intended by a "terminus beginning at", because use of the word "beginning makes it unclear what is and is not intended to be embraced by the term "terminus." It is suggested that the claim should be rewritten to be drawn to a substantially pure nucleic acid encoding a fragment of the polypeptide of SEQ ID NO:4, wherein the C-terminus of the fragment is at position 284 of SEQ ID NO:4, and the N-terminus of the fragment is at any one of amino acids 81-139 of SEQ ID NO:4.

Claim 53, 62, 63, and 65-67 dependents are indefinite in the recitation of "the complement of said coding sequence is selected from ... a) nucleotides 106-852 of SEQ ID NO:3: and b) nucleotides 241-852 of SEQ ID NO:3", because SEQ ID NO:3 is not the complement of a coding sequence.

Claims 60, 62 and 63 are indefinite in the recitation of "the complement of said coding sequence is selected from ... a) SEQ ID NO:1: and b) nucleotides 65-676 of SEQ ID NO:1", because SEQ ID NO:1 is not the complement of a coding sequence.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 57-60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 57-59 are drawn to nucleic acids encoding a polypeptide having an amino acid terminus at beginning at any one of amino acids 22 to 80 of SEQ ID NO:2. There is no written support for this limitation in the specification as filed, so it constitutes new matter. At page 19 of the response, Applicant points for support to specification pages 7 and 16, and Fig. 1. However, none of these passages provides support for the recited limitation.

Claim 60 is drawn to a nucleic acid that hybridizes to nucleotides 65-676 of SEQ ID NO:1. There is no written support for this limitation in the specification as filed, so it constitutes new matter. At page 20 of the response, Applicant points for support to specification pages 7, 8, 16, 30, 34 and Fig. 1. However, none of these passages provides support for the recited limitation.

Written Description

Claims 51-53, 55, 58-63, and 65-67 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 51 and 52 and dependents are drawn to nucleic acids encoding polypeptides that are at least 90 or 95% identical, respectively, to SEQ ID NO:4. SEQ ID NO:4 comprises a human TRELL polypeptide. It is unclear what is the N-terminus of the polypeptide, but it may be at position 1 or position 36 of SEQ ID NO:4. See e.g. page 14, lines 32 and 33. Claim 53 and dependents are drawn to a nucleic acid that hybridizes under high stringency conditions to bases 106-852 or 241-852 of SEQ ID NO:3. SEQ ID NO:3 is a nucleic acid encoding SEQ ID NO:4. Claims 62, 63, 65, and 66 depend in part from claims 51 and 53. Claim 67 embraces host cells comprising a nucleic acid of claims 51-53.

The specification discloses a single species of these claimed genuses, i.e. SEQ ID NO:3. Note that SEQ ID NO:2, which is a fragment of mouse TRELL, is less than 90% identical to SEQ ID NO:4, and so SEQ ID NO:1 is not a member of the genuses claimed in claims 51-53 because it does not encode a polypeptide that is at least 90% identical to SEQ ID NO:4.

The specification discloses at page 36 that human TRELL has the property of inducing apoptosis in HT-29 cells. The specification fails to provide any guidance as to the relationship between the structure of TRELL and this function or any other disclosed function. In particular, there is no guidance as to how the sequence of the single disclosed species of the claimed genus can be varied while still retaining its function, and no specific examples are given of any such variant. In view of the large number of

conceivable variants in the claimed genus, and the failure to provide any correlation between the structure of TRELL and any function, one of skill in the art could not conclude that Applicant was in possession of the claimed genus at the time of filing.

Claim 55 is drawn to a nucleic acid encoding a polypeptide comprising SEQ ID NO:2. As discussed above, SEQ ID NO:2 is encoded by SEQ ID NO:1 which is a partial cDNA. This is apparent because SEQ ID NO:2 corresponds to amino acids 60-284 of human TRELL (SEQ ID NO:4), and encodes only a partial transmembrane domain, and no N-terminal cytoplasmic domain. See e.g. Fig 1. Claim 55 embraces a full-length cDNA encoding a polypeptide comprising SEQ ID NO:2, but the specification fails to adequately describe such a molecule. The courts have found that merely describing the functional characteristics of a protein encoded by a particular nucleic acid is insufficient to adequately describe the genus of nucleic acids encoding that protein. A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. See Oka, 849 F.2d at 583, 7 USPQ2d at 1171. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by a principal biological property, e.g., binding to cells that bind SEQ ID NOS:2 or 4, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. When an inventor is unable to envision the detailed constitution of a

gene so as to distinguish it from other materials, conception has not been achieved until reduction to practice has occurred, i.e., until after the gene has been isolated. *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). The instant application does not provide a written description that would allow one of skill in the art to immediately envisage the specific structure for the full length mouse cDNA of TRELL. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed* (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As there disclosure of only a single species of the polynucleotides, the skilled artisan cannot envision the detailed chemical structure of the claimed genus, particularly of the full length cDNA, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of any method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

It is noted that claim 56, drawn to a nucleic acid encoding a polypeptide consisting essentially of SEQ ID NO:2, is not included in this rejection because it uses

the transitional phrase "consisting essentially of" rather than "comprising". Regarding this phrase MPEP 2163 states:

> "By using the term 'consisting essentially of,' the drafter signals that the invention necessarily includes the listed ingredients and is open to unlisted ingredients that do not materially affect the basic and novel properties of the invention. A consisting essentially of' claim occupies a middle ground between closed claims that are written in a consisting of' format and fully open claims that are drafted in a comprising' format." PPG Industries v. Guardian Industries, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998).

For this reason, claim 56 is not considered to embrace a full-length mouse cDNA, and is adequately described.

Claim 58 and dependents are drawn to a nucleic acid encoding a polypeptide at least 90% identical to a polypeptide consisting essentially of SEQ ID NO:2 or a polypeptide having an amino terminus beginning at any one of amino acids 22-80 of SEQ ID NO:2. SEQ ID NO:2 is a fragment of mouse TRELL. Claim 59 further limits claim 58 by requiring 95% identity. Claim 60 an dependents are drawn to a nucleic acid encoding a polypeptide, wherein the nucleic acid hybridizes under highly stringent conditions to SEQ ID NO:1 or nucleotides 65-676 of SEQ ID NO:1. SEQ ID NO:1 is a partial cDNA encoding a fragment (SEQ ID NO: 2) of mouse TRELL.

The specification fails to provide any guidance as to the relationship between the structure of mouse TRELL and any function. In particular, there is no guidance as to how the sequence of the single disclosed species of the claimed genus can be varied while still retaining any function, and no specific examples are given of any such variant. In view of the large number of conceivable variants in the claimed genus, and the failure to provide any correlation between the structure of TRELL and any function, one of skill

in the art could not conclude that Applicant was in possession of the claimed genus at the time of filing.

Scope of Enablement

Claims 51-53, 55, 58-63, 65-67, 84, 96, and 97 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acid molecules encoding SEQ ID NOS:2 or 4, and for isolated host cells comprising these nucleic acids, does not reasonably provide enablement for nucleic acid molecules encoding variants of SEQ ID NOS:2 or 4 which comprise one or more amino acid substitutions relative to SEQ ID NOS: 2 and 4, and does not reasonably provide enablement for host cells in vivo comprising nucleic acids encoding SEQ ID NOS: 2 or 4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 51-53, 55, 58-63, and 65-67are drawn to nucleic acids encoding variants of the polypeptides of SEQ ID NOS:2 or 4. SEQ ID NO:2 comprises the amino acid sequence of mouse TRELL, SEQ ID NO:4 comprises the amino acid sequence of human TRELL. The variants may be 90% or 95% identical to SEQ ID NOS: 2 or 4 or particular fragments thereof. See e.g. claims 51, 52, 58, and 59. Alternatively the nucleic acids may hybridize to nucleic SEQ ID NOS: 1 or 3 under particular highly stringent conditions. See e.g. claims 53, 60, and 61. Thus the claims embrace nucleic acids encoding polypeptides that may vary substantially from the disclosed amino acid sequences of SEQ ID NOS:2 and 4.

The specification teaches the polynucleotides of SEQ ID NOS 1 and 3, which encode amino acid sequences of SEQ ID NOS: 2 and 4. The specification also teaches

the construction of a form of human TRELL lacking the transmembrane region of TRELL, and consisting of some fraction of the extracellular TRELL domain of TRELL linked to a secretion signal and a myc epitope tag. See pages 34 and 35. The specification discloses that human TRELL causes apoptosis in HT-29 cells, but not in several other tumor lines. See page 36 and Table II on page 37.

Pertinent to the variant forms of TRELL encompassed by the rejected claims, the specification teaches at page 1 that the family of TNF-related cytokines comprises at least 9 different receptor-ligand pairs that have an amino acid sequence-relatedness of about 50%. These molecules have disparate functions ranging from stimulation of apoptosis to stimulation of cell division. The specification gives general guidance as to broad structural features of the prior art molecules, e.g. transmembrane domains, extracellular and intracellular domains, and a cysteine-rich ligand binding domain that is formed through oligomerization of subunits. However, no guidance is offered relative to what specific amino acids are required for any particular function. It is also worth noting that SEQ ID NOS: 2 and 4 differ from the prior art polypeptides in that they do not appear to have any cysteine-rich ligand binding domain, so it is unclear if they form oligomers. Further, the specification discloses that the ligands for SEQ ID NOS: 2 and 4 are unknown, as are their biological functions. See e.g. sentence bridging page 4 and 5. Although the specification demonstrates that human TRELL can induce apoptosis in HT-29 cells, it fails to teach what amino acids are required for this or any other function, or what amino acid substitutions will preserve this or any other function. In view of the variety of structures and functions within the TNF-related cytokine family, and the lack of guidance regarding the structure and function of SEQ ID NOS: 2 and 4, it is highly unpredictable as to how amino acid substitution will affect the functions of SEQ ID NOS: 2 and 4. The prior art teaches generally that the effects of amino acid substitutions and

deletions on protein function are highly unpredictable. Rudinger (In Peptide Hormones J.A. Parsons, Ed. University Park Press, Baltimore, 1976, page 6) taught that "[t]he significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study." Ngo et al (In The Protein Folding Problem and Tertiary Structure Prediction, K. Merz Jr. and S. Legrand, Eds. Birkhauser, Boston, 1994, see page 492) taught that "[i]t is not known if there exists an efficient algorithm for predicting the structure of a given protein from its amino acid sequence alone. Decades of research have failed to produce such an algorithm". One might argue that it would not be undue experimentation to express and assay polypeptides individually, and thereby empirically determine the function of each one. However as set forth in *In Re Fisher*, 166 USPQ 18(CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and **their performance characteristics predicted by resort to known scientific laws**; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with the degree of unpredictability of the factors involved.

Emphasis added. Taken together, the teachings of the prior art indicate that substitutions in SEQ ID NOS: 2 and 4 may produce inactive proteins, and that the functions of altered versions of SEQ ID NOS: 2 and 4 are highly unpredictable. Because the effects of alterations to SEQ ID NOS:2 and 4 are unpredictable, and because the specification fails to teach which specific alterations can be made without abolishing TRELL activity, one of skill in the art could not make the claimed nucleic acids, other than those encoding polypeptides comprising SEQ ID NOS:2 or 4, or active fragments thereof without undue experimentation.

Claims 84, 96, and 97 are drawn to host cells comprising nucleic acids encoding SEQ ID NOS: 2 or 4. It is readily apparent that these host cells may be used in vitro for the production of the TRELL protein and for its subsequent use in studying apoptosis of HT-29 cells. However, the specification also teaches that host cells in vivo that express TRELL for the purpose of gene therapy, e.g. at page 13, lines 16-22. This rejection pertains to the scope of the claims that embraces host cells in vivo.

The specification provides very limited guidance regarding methods of gene therapy, generally disclosing that the claimed DNA sequences can be used to express TRELL under abnormal conditions. The sequences could be expressed in tumor cells under the direction of promoters appropriate for such applications and such expression could enhance anti-tumor immune responses or directly affect the survival of the tumor. In addition, the sequences can be used to affect the survival of an organ graft by altering the local immune response (see page 13 of the specification). However, the specification does not disclose abnormal conditions, other than cancer or organ graft, which can be treated by expressing a polynucleotide encoding TRELL. The specification also fails to disclose the types of tumors in a patient which could be treated by expressing a polynucleotide encoding TRELL, or any alterations in the local immune response as a function of the expression of a polynucleotide encoding TRELL. The specification does not disclose appropriate promoters to use, appropriate target sites for delivery of the polynucleotide, appropriate expression vectors required in the delivery of the polynucleotide, or the level of expression of the polynucleotide such that an anti-tumor response or an alteration in the local immune response is achieved. It is further noted that the specification discloses that only one cell line of eleven cell lines tested *in vitro* displayed any response to a TRELL peptide, and this response required the presence of interferon-gamma (see Table II on page 37 of the instant application).

Clearly, the showing in the specification is not sufficient to solve the art-recognized problems associated with gene therapy, as set forth by Verma and Orkin (see Paper Nos. 11 and 15). Thus, as stated in the Paper Nos. 11 and 15, the specification is non-enabling for gene therapy protocols as the specification does not disclose methods by which the skilled artisan could predictably and reproducibly introduce and express TRELL polynucleotides in a mammal for therapeutic effect of any disease or disorder. This portion of the rejection may be overcome by limiting claims 84, 96, and 97 to isolated host cells.

Conclusion

Claims 48, 49, 54, 56, 64, 75-83, 86-90, 92-95, 98, and 99 are allowable.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax number is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Richard Schnizer, Ph.D.